Ageing with HIV: medication use and risk for potential drug-drug interactions

Marzolini, C ; Back, D ; Weber, R ; Furrer, H ; Cavassini, M ; Calmy, A ; Vernazza, P ; Bernasconi, E ; Khoo, S ; Battegay, M ; Elzi, L

Abstract: OBJECTIVES: To compare the use of co-medication, the potential drug-drug interactions (PDDIs) and the effect on antiretroviral therapy (ART) tolerability and efficacy in HIV-infected individuals according to age, 50 years or <50 years. METHODS: All ART-treated participants were prospectively included once during a follow-up visit of the Swiss HIV Cohort Study. Information on any current medication was obtained by participant self-report and medical prescription history. The complete treatment was subsequently screened for PDDIs using a customized version of the Liverpool drug interaction database. RESULTS: Drug prescriptions were analysed for 1497 HIV-infected individuals: 477 age 50 and 1020 age <50. Older patients were more likely to receive one or more co-medications compared with younger patients (82% versus 61%; $P < 0.001$) and thus had more frequent PDDIs (51% versus 35%; $P < 0.001$). Furthermore, older patients tended to use a higher number of co-medications and certain therapeutic drug classes more often, such as cardiovascular drugs (53% versus 19%; $P < 0.001$), gastrointestinal medications (10% versus 6%; $P = 0.004$) and hormonal agents (6% versus 3%; $P = 0.04$). PDDIs with ART occurred mainly with cardiovascular drugs (27%), CNS agents (22%) and methadone (6%) in older patients and with CNS agents (27%), methadone (15%) and cardiovascular drugs (11%) in younger patients. The response to ART did not differ between the two groups. CONCLUSIONS: The risk for PDDIs with ART increased in older patients who take more drugs than their younger HIV-infected counterparts. However, medication use in older and younger patients did not differ in terms of effect on antiretroviral tolerability and response.

DOI: https://doi.org/10.1093/jac/dkr248

J Antimicrob Chemother 2011; **66**: 2107–2111
doi:10.1093/jac/dkr248 Advance Access publication 16 June 2011

Journal of Antimicrobial Chemotherapy

Ageing with HIV: medication use and risk for potential drug–drug interactions

Catia Marzolini[1]*, David Back[2], Rainer Weber[3], Hansjakob Furrer[4], Matthias Cavassini[5], Alexandra Calmy[6], Pietro Vernazza[7], Enos Bernasconi[8], Saye Khoo[2], Manuel Battegay[1] and Luigia Elzi[1] on behalf of the Swiss HIV Cohort Study†

[1]Division of Infectious Diseases and Hospital Epidemiology, University Hospital Basel, Basel, Switzerland; [2]Pharmacology Research Laboratories, University of Liverpool, Liverpool, UK; [3]Division of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich, Zurich, Switzerland; [4]Division of Infectious Diseases, Bern University Hospital and University of Bern, Bern, Switzerland; [5]Division of Infectious Diseases, University Hospital Lausanne, Lausanne, Switzerland; [6]Division of Infectious Diseases, University Hospital Geneva, Geneva, Switzerland; [7]Division of Infectious Diseases and Hospital Epidemiology, Cantonal Hospital St Gallen, St Gallen, Switzerland; [8]Division of Infectious Diseases, Regional Hospital Lugano, Lugano, Switzerland

*Corresponding author. Tel: +41-61-265-47-46; Fax: +41-61-265-31-98; E-mail: marzolinic@uhbs.ch
†Members of the Swiss HIV Cohort Study are listed in the Acknowledgements section.

Received 1 April 2011; returned 5 May 2011; revised 9 May 2011; accepted 20 May 2011

Objectives: To compare the use of co-medication, the potential drug–drug interactions (PDDIs) and the effect on antiretroviral therapy (ART) tolerability and efficacy in HIV-infected individuals according to age, ≥50 years or <50 years.

Methods: All ART-treated participants were prospectively included once during a follow-up visit of the Swiss HIV Cohort Study. Information on any current medication was obtained by participant self-report and medical prescription history. The complete treatment was subsequently screened for PDDIs using a customized version of the Liverpool drug interaction database.

Results: Drug prescriptions were analysed for 1497 HIV-infected individuals: 477 age ≥50 and 1020 age <50. Older patients were more likely to receive one or more co-medications compared with younger patients (82% versus 61%; $P<0.001$) and thus had more frequent PDDIs (51% versus 35%; $P<0.001$). Furthermore, older patients tended to use a higher number of co-medications and certain therapeutic drug classes more often, such as cardiovascular drugs (53% versus 19%; $P<0.001$), gastrointestinal medications (10% versus 6%; $P=0.004$) and hormonal agents (6% versus 3%; $P=0.04$). PDDIs with ART occurred mainly with cardiovascular drugs (27%), CNS agents (22%) and methadone (6%) in older patients and with CNS agents (27%), methadone (15%) and cardiovascular drugs (11%) in younger patients. The response to ART did not differ between the two groups.

Conclusions: The risk for PDDIs with ART increased in older patients who take more drugs than their younger HIV-infected counterparts. However, medication use in older and younger patients did not differ in terms of effect on antiretroviral tolerability and response.

Keywords: HIV/AIDS, older patients, polypharmacy, drug–drug interactions, cardiovascular drugs

Introduction

HIV-infected individuals are becoming older as a result of reduced AIDS-related mortality due to combination antiretroviral therapy (ART).[1] It is projected that by 2015, more than half of all HIV-infected individuals in the USA will be ≥50 years of age.[2] Compared with age-matched HIV-uninfected individuals and with younger HIV-infected individuals, HIV-infected people ≥50 years have a higher rate of co-morbidities such as cardiovascular disease, metabolic disorders, osteoporosis, non-HIV cancers, hepatic and renal impairments, possibly exacerbated by HIV infection or long-term exposure to ART.[3] Consequently, the management of HIV infection in older patients is complicated by polypharmacy, which may increase the rate of potential drug–drug interactions (PDDIs) with antiretroviral therapy as well

as drug toxicity.[4] Our aim was to compare the use of co-medication, the risk for PDDIs and the effect on ART tolerability and virological suppression in older versus younger HIV-infected individuals.

Methods

The data for this analysis were collected in the framework of a cross-sectional study aimed at investigating the prevalence of PDDIs among the patients of the Swiss HIV Cohort Study (SHCS).[5] Briefly, the study prospectively included all ART-treated patients scheduled for an SHCS follow-up visit once from April 2008 to January 2009. Information on current medication was obtained by patient self-report and medical prescription history. The drugs documented included ART, co-medications used for opportunistic infections and concurrent diseases, as well as self-prescribed drugs, herbals and recreational drugs. The complete treatment was screened for PDDIs using a customized version of the University of Liverpool drug interaction database,[6] and interactions were subsequently validated by two experts in HIV pharmacology. The Liverpool drug interaction database features interactive charts to assess the risk of drug interactions between HIV–HIV drugs and HIV–non-HIV drugs. These charts rank the clinical significance of an interaction from 'no interaction' to 'dose adaptation' and 'contraindicated'.[6]

Potentially clinically relevant drug interactions were defined as all drug interactions involving an HIV drug and requiring dose adjustment or contraindicated drug combinations. Conversely, drug interactions were not counted as clinically significant if the appropriate dose adaptation had already been performed, if the change in pharmacokinetic parameters was less than 25% and/or if the interaction was reported as clinically irrelevant. Interactions between non-HIV medications were excluded from this analysis.

Information on socio-demographic characteristics, data on the clinical course, co-infection with hepatitis B or C, immunological and viral parameters were extracted from the SHCS database at the time of co-medication assessment. Additional data on the virological and immunological outcomes as well as the rate of treatment change or discontinuation because of toxicity or adverse events were obtained after 6–12 months of follow-up. Viral suppression was defined as an HIV viral load of <50 copies/mL.

The SHCS was approved by the relevant ethics committees of the participating centres, and written consent was obtained from all study participants.

For the statistical analysis, patients were grouped as 'older patients' (≥50 years) and 'younger patients' (<50 years) based on the CDC definition of older HIV patients.[7] Basic socio-demographic characteristics, CD4 cell count, HIV viral load, ART regimens and co-medication were compared using the χ^2 test or Fisher's exact test for categorical variables, and the Mann–Whitney test for continuous variables. All analyses were performed using STATA software version 11 for Windows.

Table 1. General characteristics of the study population ($n=1497$) according to age

Characteristics	Age <50 years ($n=1020$)	Age ≥50 years ($n=477$)	*P*
Males	625 (61)	383 (80)	<0.001
Median body mass index, kg/m^2 (IQR)	23 (21–26)	24 (22–26)	<0.001
Non-white ethnicity	263 (26)	25 (5)	<0.001
Transmission risk			
MSM	293 (29)	209 (44)	<0.001
heterosexual	466 (46)	196 (41)	
IDU	261 (26)	72 (15)	
Current IDU	43 (4)	8 (2)	0.012
Current recreational drug use	216 (21)	48 (10)	<0.001
Prior AIDS-defining condition	281 (28)	156 (33)	0.041
Education			
low	334 (33)	87 (18)	<0.001
middle	444 (44)	238 (50)	
high	226 (22)	143 (30)	
HCV co-infection	297 (29)	88 (19)	<0.001
HBV co-infection (HBs-antigen positive)	43 (4)	29 (6)	0.116
ART naive	133 (13)	40 (8)	0.009
Co-medication	624 (61)	389 (82)	<0.001
Interaction	357 (35)	242 (51)	<0.001
Median CD4 cell count, cells/mm^3 (IQR)	513 (361–702)	493 (355–658)	0.126
HIV RNA <50 copies/mL	853 (84)	417 (87)	0.062
Class			
PI	507 (50)	186 (39)	<0.001
NNRTI	367 (36)	207 (43)	
PI+NNRTI	57 (6)	40 (8)	
other	89 (9)	44 (9)	
Backbone			
TDF/FTC or TDF/3TC	417 (41)	188 (39)	0.302
ABC/3TC	194 (19)	78 (16)	
ZDV/3TC	126 (12)	63 (13)	
other	185 (18)	103 (22)	

ABC, abacavir; 3TC, lamivudine; FTC, emtricitabine; TDF, tenofovir; ZDV, zidovudine; IDU, intravenous drug user; IQR, interquartile range.
Data are presented as number (%) of patients, unless otherwise indicated.

Results

The analysis included 1497 ART-treated patients, among whom 477 (32%) and 1020 (68%) were ≥50 years and <50 years, respectively. Older and younger patients differed in terms of socio-demographic characteristics, mode of HIV transmission, co-infection and use of co-medication (Table 1). Older HIV patients were more likely to be male, Caucasian and have a higher body mass index. Men having sex with men (MSM) was the main mode of HIV transmission in the group of older patients. The presence of a prior AIDS-defining condition and pre-treatment with antiretroviral therapy were more common in older patients. A higher percentage of drug addiction and co-infection with hepatitis C virus (HCV) was observed in the group of younger HIV patients. The median CD4 cell count and the percentage of patients virally suppressed did not differ substantially between older and younger HIV patients (493 versus 513 cells/mm^3; $P=0.126$ and 87% versus 84%; $P=0.062$, respectively).

Older HIV patients were more likely to receive one or more co-medications compared with younger patients [82%

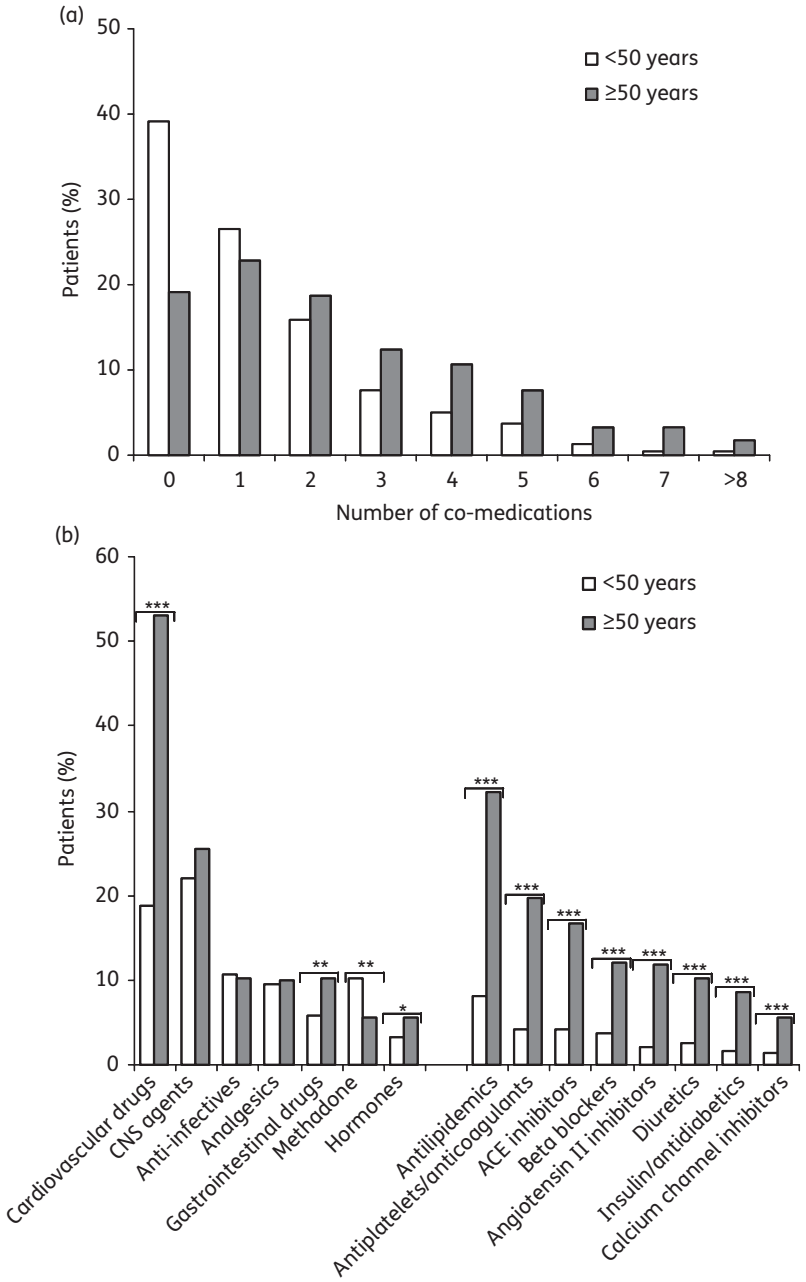

Figure 1. Number of co-medications (a) and therapeutic drug classes (b) used in patients age <50 years or ≥50 years. (b) Each bar represents the percentage of patients using one or more drugs of the corresponding therapeutic class. Detailed use of cardiovascular drugs is presented in the right-hand half of the figure. CNS agents included anxiolytics/sedatives, antidepressants, antipsychotics and anticonvulsants. Anti-infectives included antibacterials, antivirals, antifungals and antimycobacterials. Analgesics included anti-inflammatory drugs, paracetamol and narcotic analgesics. Gastrointestinal drugs included proton pump inhibitors, antidiarrhoea drugs and H_2 blockers. *$P<0.05$, **$P<0.01$, ***$P<0.001$.

(389/477) versus 61% (624/1020); $P<0.001$] and thus had more frequent PDDIs [51% (242/477) versus 35% (357/1020); $P<0.001$] (Table 1). Furthermore, older patients tended to use a higher number of co-medications {median number of co-medications 2 [interquartile range (IQR) 1–4)] versus 1 [IQR 0–2]} (Figure 1a) and certain therapeutic drug classes more often than younger patients (Figure 1b), such as cardiovascular drugs (53% versus 19%; $P<0.001$), gastrointestinal medications (10% versus 6%; $P=0.004$) and hormonal agents (6% versus 3%; $P=0.04$). Conversely, younger patients more often received methadone (10% versus 6%; $P=0.002$). No differences in use of CNS agents, anti-infectives and analgesics were seen between the two groups (Figure 1b).

Among the older patients with co-medication, PDDIs were mainly between protease inhibitors (PIs) or non-nucleoside reverse transcriptase inhibitors (NNRTIs) and cardiovascular

drugs (27%), CNS agents (22%) and methadone (6%). Among the younger patients with co-medication, PDDIs occurred mainly between CNS agents (27%), methadone (15%) and cardiovascular drugs (11%). In the majority of PDDIs the antiretroviral affected the co-medication rather than the co-medication affecting the antiretroviral. Therefore, there was no difference in virological suppression (90% in older and 85% in younger subjects with PDDIs; $P=0.093$).

A change in ART because of toxicity, defined as any clinical or serious laboratory adverse events, was performed in 4% of older versus 3% of younger patients with PDDIs ($P=0.374$). The type of toxicity was similar in both groups ($P=0.314$) and was mostly characterized by gastrointestinal intolerance, followed by CNS-related side effects, hepatotoxicity and dyslipidaemia.

Discussion

Little is known about the impact of ageing on medication use in HIV-infected patients, the potential interactions of co-medications with ART and the effect on antiretroviral therapy tolerability and virological outcome. We found that the risk for PDDIs increases in older patients who take more drugs than their younger HIV-infected counterparts. In the present study, certain therapeutic classes, mainly cardiovascular drugs, and to a lesser extent gastrointestinal and hormonal agents, were more often used in older patients, in agreement with previous surveys from Italy and Canada.[8–10] The higher proportion of cardiovascular drugs in older patients may result from prolonged exposure to ART, which has been correlated with increased cardiovascular risk.[11] In addition, age constitutes an important risk factor for the development of metabolic disorders and, ultimately, for increased cardiovascular risk.

Since PDDIs were primarily related to ART acting on the co-medication,[5] no adverse effects were noted on ART tolerability or efficacy. This suggests that specific therapeutic drug classes used in elderly patients were not *per se* a risk factor for impaired response to ART.

Besides medication use, older and younger patients differed in terms of mode of HIV infection. The higher rate of HIV transmission through homosexual contacts observed in older patients may be explained by the fact that HIV infection was more prevalent among MSM in the early years of the epidemic.

Our study has some limitations. The dose or eventual dose adjustment of co-medications was not systematically reported, which may have influenced the tolerability results. Toxicities resulting from PDDIs were not assessed through laboratory abnormalities. However, we considered all side effects that were serious enough to require a treatment change. The cross-sectional design of the study did not allow us to determine whether co-morbidities were present before HIV infection or developed during the course of the disease or following initiation of antiretroviral therapy.

With the ever-increasing number of older patients, future research will be instrumental in addressing issues of drug–drug interactions, risk of toxicity and the impact of polypharmacy on adherence.

Acknowledgements

This study was presented in part at the Tenth International Congress on Drug Therapy in HIV Infection, Glasgow, 2010 (oral presentation 0:26).

Swiss HIV Cohort Study (SHCS) members

M. Battegay, E. Bernasconi, J. Böni, H. C. Bucher, P. Bürgisser, A. Calmy, S. Cattacin, M. Cavassini, R. Dubs, M. Egger, L. Elzi, M. Fischer, M. Flepp, A. Fontana, P. Francioli (president of the SHCS), H. Furrer (chairman of the Clinical and Laboratory Committee), C. Fux, M. Gorgievski, H. Günthard (chairman of the Scientific Board), H. H. Hirsch, B. Hirschel, I. Hösli, Ch. Kahlert, L. Kaiser, U. Karrer, C. Kind, Th. Klimkait, B. Ledergerber, G. Martinetti, B. Martinez, N. Müller, D. Nadal, M. Opravil, F. Paccaud, G. Pantaleo, A. Rauch, S. Regenass, M. Rickenbach (head of the Data Center), C. Rudin (chairman of the Mother & Child Substudy), P. Schmid, D. Schultze, J. Schüpbach, R. Speck, P. Taffé, P. Tarr, A. Telenti, A Trkola, P. Vernazza, R. Weber and S. Yerly.

Funding

This study has been financed in the framework of the SHCS, supported by the Swiss National Science Foundation (grant 108787). C. M. has been supported by a grant from the Swiss National Science Foundation (Marie Heim-Vögtlin subsidy PMPDP3-122791/1). L. E. received an unrestricted research grant from the Department of Medicine, University Hospital Basel. The authors affirm the independence of the researchers from the funders.

Transparency declarations

D. B. and S. K. have received research grants, travel support and honoraria from Gilead, Bristol-Myers Squibb, Boehringer Ingelheim, Tibotec, ViiVHealthcare and Merck. R. W. has received travel grants or speaker's honoraria from Abbott, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, ViiVHealthcare, Merck Sharp & Dohme, Roche, TRB Chemedica and Tibotec. H. F. has participated on advisory boards of ViiVHealthcare, Bristol-Myers Squibb, Gilead, Merck Sharp & Dohme, Boehringer Ingelheim and Janssen, and H. F.'s institution has received unrestricted educational grants from Abbott, ViiVHealthcare, Bristol-Myers Squibb, Roche, Gilead, Merck Sharp & Dohme, Boehringer Ingelheim, Essex and Janssen. M. C. has received travel grants from Abbott, Boehringer Ingelheim, Gilead and Roche. E. B. has received honoraria or travel grants from Abbott Laboratories, Boehringer Ingelheim, Gilead, ViiVHealthcare, Merck Sharp & Dohme and Tibotec. M. B. has received speaker's honoraria from Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, ViiVHealthcare, Merck Sharp & Dohme and Tibotec; has received unrestricted research grants from Boehringer Ingelheim, Gilead and ViiVHealthcare; and serves as a consultant for Boehringer Ingelheim Switzerland. C. M., A. C., P. V. and L. E. declare that they have no conflicts of interest.

Author contributions

C. M., D. B., S. K., M B. and L. E. designed the study. C. M. and E. L. analysed the data. L. E. conducted the statistical analyses. R. W., H. F., M. C., A. C., P. V., E. B., M. B. and L. E. were responsible for the recruitment and clinical assessment of patients. C. M. and L. E. wrote the report, assisted by all co-authors. All authors have read and approved the final version.

References

1 Antiretroviral therapy cohort collaboration. Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analysis of 14 cohort studies. *Lancet* 2008; **372**: 293–9.

2 Effros RB, Fletcher CV, Gebo K *et al*. Workshop on HIV infection and aging: what is known and future research directions. *CID* 2008; **47**: 542–53.

3 Nkhoma E, Vannappagari V, Mynepalli L *et al*. Comorbidities and coinfections among HIV patients 50 years and older. *In: Abstracts of the First International Workshop on HIV & Aging, Baltimore, MD, 2010*. Abstract O_16.

4 Simone MJ, Appelbaum J. HIV in older adults. *Geriatrics* 2008; **63**: 6–12.

5 Marzolini C, Elzi L, Gibbons S *et al*. Prevalence of comedications and effect of potential drug-drug interactions in the Swiss HIV Cohort Study. *Antiviral Therapy* 2010; **15**: 413–23.

6 Liverpool HIV Drug Interactions web site. http://www.hiv-druginteractions.org (20 January 2011, date last accessed).

7 CDC. http://www.cdc.gov/hiv/topics/over50/ (20 January 2011, date last accessed).

8 Tseng A, Raboud J, Walmsley S *et al*. Polypharmacy in older patients: a study of medication use and potential drug interactions in an aging ambulatory HIV clinic population. In: *Abstracts of the First International Workshop on HIV & Aging, Baltimore, MD, 2010*. Abstract O_08.

9 Orlando G, Meraviglia P, Cordier L *et al*. Antiretroviral treatment and age-related comorbidities in a cohort of older HIV-infected patients. *HIV Medicine* 2006; **7**: 549–557.

10 Guaraldi G, Menozzi M, Zona S *et al*. Polypharmacology for polyphatology in HIV infected patients. In: *Abstracts of the First International Workshop on HIV & Aging, Baltimore, MD, 2010*. Abstract O_09.

11 Data Collection on Adverse Events of Anti-HIV Drugs (DAD) Study Group. Combination antiretroviral therapy and the risk of myocardial infarction. *NEJM* 2003; **349**: 1993–2003.